## REMARKS

Claims 1-6 and 8-22 are currently pending. Solely to facilitate prosecution and without prejudice or disclaimer, Applicant has amended claim 1 to indicate that the label to be detected is added to the complexes present in steps (a), (b), or (c) and does not form part of the carrier. Support for this amendment may be found in the specification at pages 7-9. Claim 15 has been amended to further clarify the invention. This amendment is supported in the specification at page 11, lines 10-25. Applicant has also amended claims 6 and 17 to include a second separation step. The specification supports the amendment of claims 6 and 17 at page 7, lines 29-34 and original claim 7. Claim 8 has been amended to remove dependency on canceled claim 7. Applicant has amended claims 21 and 22 to parallel the amendment made to claim 1.

Applicant acknowledges that the Office has withdrawn its previous objection to claims 10-16, 21, and 22 for alleged improper multiple dependency; its previous rejection of claims 1 and 8 as allegedly not enabled; its previous rejection of claims 1-20 as allegedly indefinite; its rejection of claims 21 and 22 as allegedly improper process claims; its previous rejection of claims 1-14, 16, and 20 as allegedly anticipated by Johansen et al. (U.S. Pat. 6,087,188; "Johansen"); and its prior rejection of claims 1 and 17-19 as allegedly anticipated by Frank et al. (U.S. Pat. 5,945,294; "Frank"). Applicant now addresses each of the Office's new claim rejections below.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Office rejects claims 6, 7, and 17-19 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Applicant notes that claim 7 is canceled. Regarding

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independent claims 6 and 17, the Office believes that a separation step to remove non-complexed labels is missing. Solely to facilitate prosecution and without prejudice or disclaimer, Applicant has amended claims 6 and 17 to include a second separation step. Applicant has now rendered the Office's rejection of claims 6 and 17-19 moot and requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 10-19, 21, and 22 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Regarding independent claim 1, the Office believes that a step introducing the label mentioned in step (d) should be added to the claim. Solely to clarify the invention and without prejudice or disclaimer, Applicant has amended claim 1 to indicate that the label to be detected is added to the complexes present in steps (a), (b), or (c) and does not form part of the carrier. As discussed in the specification at pages 7-9, the label may be introduced at several steps of the method recited in claim 1. As the Office's rejection of claim 1 and dependent claims 10-16 is moot, Applicant requests that the Office withdraw this rejection.

Regarding independent claim 17, the Office is unclear as to why, in step (d) the labeled antibodies would be specific to the complexes formed in steps (a) or (b). In claim 17, the complexes of steps (a), (b), or (c) have IgE antibody in them. The label compound introduced in step (d) of claim 17 is coupled to an anti-IgE antibody that will bind the IgE antibody present in the complexes of steps (a), (b), or (c). By binding these complexes, the anti-IgE antibody labels the complexes. See also the specification at

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page 8, line 34 to page 9, line 10. Applicant requests that the Office withdraw its rejection of claim 17 and dependent claims 18 and 19.

The Office also believes that claims 21 and 22 are confusing, because it is allegedly unclear how the method steps recited in these claims relate to the purpose as provided in the preamble of each claim. Claim 21 recites "a method of monitoring and evaluating the immunological status of a subject. . . ." As discussed in the specification at page 4, line 16 to page 5, line 5, the IgE receptors used in the claimed method have different roles in the immune response, such as antigen presentation. By employing these receptors in the method of claim 21, the method measures physiologically active IgE, those capable of binding IgE receptors, as compared to the entire population of IgE antibodies in a sample. *See* specification at page 6, lines 6-16. CD23 and FcεRI have different biological functions in the subject, including mediating allergic responses. *See* specification at page 11, lines 10-25. Thus, in detecting or quantifying the IgE populations that bind CD23 or FcεRI, the skilled artisan may obtain information on the immunological status of a subject as reflected by the biological functions of the IgE receptors.

Claim 22 recites "[a] method of monitoring and evaluating the immunological status of a subject receiving Specific Allergy Vaccination (SAV) treatment . . . ." As discussed above, use of the IgE receptors to capture IgE:ligand complexes allows the method to identify physiologically active IgE such as IgE that may take part in the allergic response. In subjects e.g. initially undergoing SAV therapy, the amount of physiologically active IgE decreases in comparison to the initial increase in total IgE. Specifically, in SAV subjects, the amount of ligand-specific IgG antibodies and other

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"interfering compounds" increases in comparison to subjects that do not receive SAV. *See* specification at page 5, lines 22-33. These ligand-specific IgGs can bind a ligand (for example an antigen), making the ligand unavailable for binding to IgE and thus decreasing the number of IgE:ligand complexes formed. Applicant notes that, with respect to claim 21, samples from subjects not receiving SAV therapy can also have interfering compounds. One example of such a subject could be one receiving therapy with IgG antibodies specific to an ligand. Other interfering compounds besides interfering immunoglobulins may be present in samples from subjects, whether receiving SAV therapy or not.

Because ligand bound to IgG or other interfering compounds will not bind to an IgE receptor, these complexes do not contribute to an allergic reaction. In contrast, IgE:ligand complexes can bind to IgE receptors and can participate in an allergic reaction. Because the ligand is in limiting supply to bind IgE, the level of IgE:ligand complexes decreases even though the entire pool of IgE in the subject's serum does not. In sum, by measuring physiologically active IgE that can bind to IgE receptors, a more accurate picture of the allergic response can be attained as compared with a method that simply measures the total pool of IgE in a subject's serum. *See* specification at page 6, lines 21-32. Applicant respectfully requests that the Office withdraw its rejection of claims 21 and 22.

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Rejection Under 35 U.S.C. § 102

Claims 1-5, 21, and 22 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Frank. Applicant previously argued that Frank's assays either required

immobilization of a component onto a substrate or fixing Frank's antigen to a plastic bead. In contrast, the instant invention uses a free, dissolved ligand. The Office now responds by asserting that the ligand bound to the plastic bead dissolves and moves freely along the flow path between the "labeling zone" and the "capture zone." According to the Office, the Ig/ligand/plastic bead complex is captured on FcεR molecules in the capture zone. In addition, the Office alleges that Frank's beads can be interpreted as part of the label. The Office concludes that Frank meets the requirement of a free, dissolved ligand. Applicant respectfully traverses.

First, because Frank's antigen is fixed to a plastic bead, a point the Office accedes, it is not a "free" ligand. Whether the bead is small enough to allow the antigen/bead complex to dissolve, is irrelevant. Frank's antigen is nonetheless tethered to a carrier agent. Applicants have amended claims 1, 21, and 22 to clarify that the label does not form part of the carrier. Thus, the Office's interpretation of Frank does not apply to the claimed invention.

Moreover, Applicant also respectfully contends that the Office's strained correlation that beads can be part of a label is in direct contradiction to the specification's teaching. Specifically, in each of the rejected claims, the carrier is bound to an IgE receptor, not the ligand. The specification at pages 10 and 11 provides examples of carriers. Among those examples is "a particulate material" such as a bead. In claim 2, the "free" ligand may be labeled. The specification also describes examples of various labels including radioactive labels, fluorescent labels, and absorbance labels. *See* specification at page 8. Applicant contends that given the specification's teaching, a skilled artisan would not consider a carrier as part of a label, especially when the

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terms "carrier" and "label" are used distinctly in the claims. As discussed above, Frank's ligand is bound to a carrier whereas the ligand as recited in the claims is a "free" ligand. Thus, Frank does not provide the element of a "free" ligand.

Second, in the method of the invention, the interactions between the sample IgE, the ligand, and the IgE receptors takes place in solution without any of these components being connected to or tethered to a support structure. *See* specification at page 5, lines 13-33. In column 14 at lines 1-5, Frank clearly states that the IgE receptor is fixed to a support structure. Applicant notes that the Office acknowledges this in its description of Frank on page 6 of the current Office Action. As discussed above, the IgE receptors of claims 1-5, 21, and 22 are bound to a carrier rather than to a support structure. Thus, Frank also does not address this aspect of the invention. Applicant respectfully requests that the Office withdraw its rejection of claims 1-5, 21, and 22 under 35 U.S.C. § 102(e) as Frank does not teach every aspect of the invention.

Rejections Under 35 U.S.C. § 103

Claims 1-5, 8-16, 21, and 22 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Johansen et al. (U.S. Patent 6,087,188; "Johansen") and in further view of Johnson et al. (U.S. Patent 6,034,066; "Johnson") and Frank et al. (U.S. Patent 6,060,326; "Frank 2"). According to the Office, Johansen teaches a method of detecting an antibody using a ligand bound to biotin; an antibody, bound to paramagnetic particles, to the antibody to be detected; and a chemiluminescent acridinium compound bound to avidin. Johnson allegedly teaches the role of CD23 in regulating the immune response, particularly IgE responses. Frank 2 allegedly teaches

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a method for detecting IgE antibodies using a human Fc epsilon receptor. The Office continues to contend that it would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson and Frank 2 to measure IgE according to the method of Johansen because CD23 and FcεRI are specific to IgE antibodies. In addition, with regard to claim 16, the Office believes it would have been obvious to use enough ligand molecules to optimize binding of all the IgE molecules in the sample. Applicant traverses.

First, regarding claim 15, Applicant has amended this claim to further clarify the invention. Amended claim 15 recites a method that uses "both the first and the second measurement as a basis for evaluating the immunological status of a subject." None of the three references cited by the Office discuss the evaluation of a patient's immunological status by measuring IgE:ligand complexes that bind to CD23 and by measuring IgE:ligand complexes that bind to FcεRI. On this basis alone, these references cannot make the invention of claim 15 obvious.

Second, with regard to claims 1-5, 8-16, 21, and 22, none of the references cited by the Office provide the requisite motivation for establishing a *prima facie* case of obviousness. As Applicant noted previously, Applicant sought to design an IgE antibody detection assay that closely simulates the *in vivo* interactions of IgE antibodies with their ligands and their receptors. To this end, Applicant has developed a detection assay that 1) uses an IgE receptor as a capture agent; 2) carries out the binding of the ligand to the target IgE antibody before or at the same time the antibody binds to an IgE receptor; 3) uses a dissolved ligand; and 4) allows binding to take place in the presence of interfering substances that may be present in the sample that contains the target IgE

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antibody. Johansen's general discussion of the assays described therein does not provide the necessary motivation to develop an assay using IgE receptors. Johnson's general discussion of the roles CD23 may play in immune responses does not motivate the skilled artisan to develop the claimed IgE detection method. Frank 2 provides no motivation for developing methods that use both a free dissolved ligand and a carrier to which is bound an IgE receptor. As such, these references cannot provide the requisite motivation.

Though Applicant has noted this deficiency in the Office's rejection previously, the Office has not yet addressed it. Applicant notes the Office's contention that, regarding claim 16, it would have been obvious to use enough ligand molecules to optimize the binding of all the IgE molecules to be detected. Again, the Office has not provided proof that any of these three references provides the motivation to do so. The Office's assertions that the invention would be obvious in lieu of a specific explanation of how these references motivate the skilled artisan to develop the claimed methods does not satisfy this requirement. Applicant therefore respectfully requests that the Office withdraw its rejection of claims 1-5, 8-16, 21, and 22.

The Office rejects claims 6, 7, and 17-20 under 35 U.S.C. § 103(a) as allegedly obvious in view of Johansen and in further view of Frank 2 and Arnold, Jr. et al. (U.S. Patent 6,004,745; "Arnold"). According to the Office, it would have been obvious to the skilled artisan to add the label molecule after a first separation step and then separating the non-complexed labels as allegedly taught in Arnold using the reagents in Johansen's method modified by Frank 2 to use FcεRI. As claim 7 is canceled, Applicant

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will address this rejection in light of claims 6 and 17-20. Applicant traverses for the following reason.

The addition of Arnold does not cure the deficiency of motivation as discussed above. The Office cites Arnold for allegedly discussing a "typical sandwich immunoassay." This assay as described by Arnold, employs antibodies that are immobilized. The claimed methods allow binding reactions between IgE and ligand to take place in solution without the involvement of an immobilizing agent. *See* specification at page 3, lines 22-30; page 5, lines 13-20. Because these methods are not comparable, Arnold cannot cure the lack of motivation, in Johansen and Frank 2, to develop the claimed methods.

Moreover, Arnold teaches away from the use of a sandwich assay. Arnold classifies a sandwich assay as being a "heterogeneous" assay, which requires separation steps to separate labeled from unlabeled substances. *See* col. 1, lines 48-51 and lines 56-67. The thrust of Arnold's invention is to develop a method that will increase sensitivity over "heterogeneous" assays by developing a "homogenous" assay. *See* col. 2, lines 14-16. "Homogenous" assays use a label that can undergo a detectable change in stability whenever a ligand binds to the labeled molecule. *See* col. 4, lines 37-41. As such, these "homogenous" assays do not require any separation steps. *See* col. 1, lines 51-52. Thus, because Arnold teaches towards methods of detecting that do not employ any separation steps, this reference teaches away from the claimed methods, which do employ at least one separation step. For these reasons, Applicant respectfully requests that the Office withdraw its rejection of claims 6 and 17-20 as obvious.

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## Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of pending claims 1-6 and 8-22.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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